Physical Manifestations Associated with Neurofibromatosis (NF-1)

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Introduction

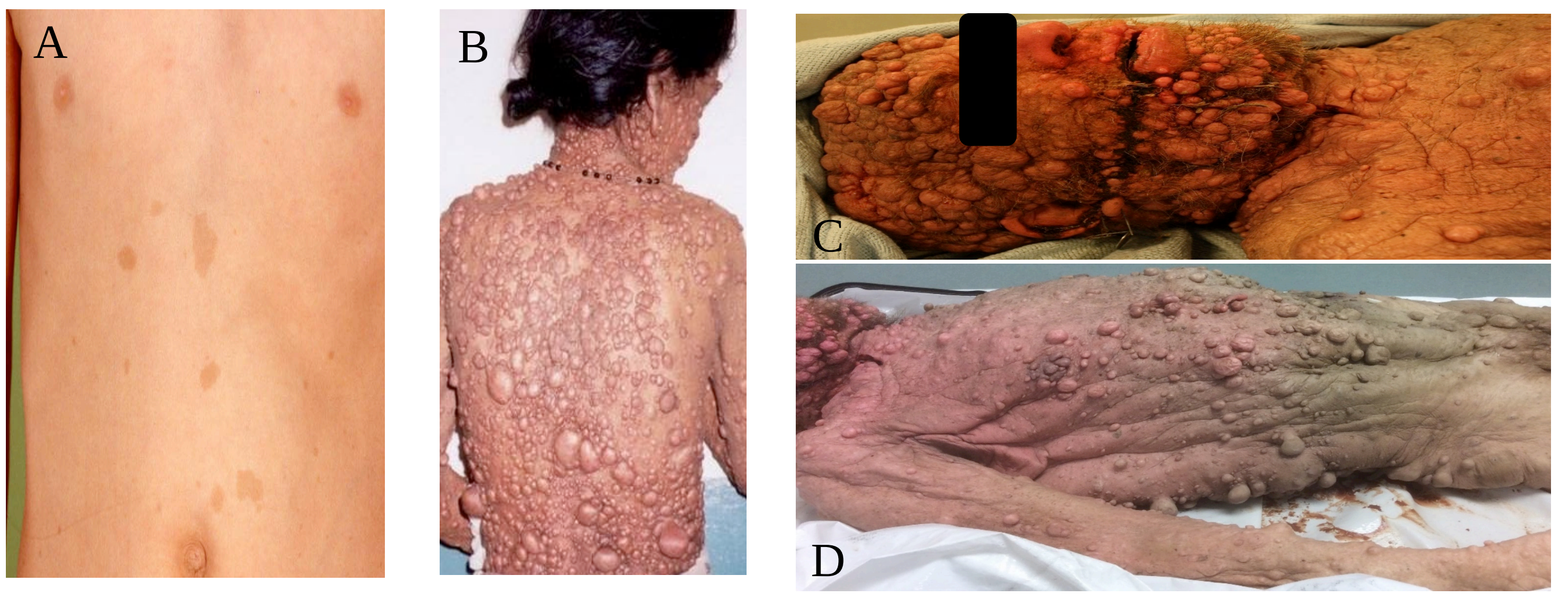
Neurofibromatosis (NF-1), know as Von Recklinghausen's disease, is one of the most common genetic disorders, affecting about 1 in 3,500 people. Inherited in an autosomal dominant fashion, this disorder results in lesions of the nervous, visual and integumentary system that are highly variable in their level of severity. NF-1 is caused by a mutation of a gene located on chromosome 17 which encodes the protein neurofibromin, a negative regulator of cell signaling pathways for the control of cellular division. Thusly, the NF gene is referred to as a tumor suppressing gene and mutations result in mostly benign tumorous growths and more rarely malignancies. NF-1 phenotypically presents itself with a variety of characteristic manifestations. While these manifestations are highly disfiguring they are generally painless and very rarely become life threatening. In addition to the neurofibromas of the central and peripheral nervous system, NF-1 may affect any part of the body resulting in a variety of complications. In this case study, we present the results of a cadaveric dissection of a donor with NF-1 to catalog the most common manifestations of this disease.

Methods for Identifying Common Manifestations of NF-1 in Donor

Symptoms	Age of Presentation	Frequency	Procedure
Café-au-lait spots[1]	Occasionally at birth; usually present by age 2	99 %	Gross examination of donor with black light
Freckling of axillary and inguinal regions[2]	Between ages 3 – 5	>90 %	Gross examination of axillary and inguinal regions of donor
Lisch nodules[3]	Late childhood / adolescence	95 %	Examination of donors iris using a dissecting scope
Optic nerve glioma[4]	Childhood, <6 years of age; may be asymptomatic	15 %	Dissection of the orbit and optic nerve
Sphenoid dysplasia[5]	Typically visible by age 1	3 – 7 %	X-rays and CT scan of skull
Tibial dysplasia[6]	Typically visible by age 1	1 – 4 %	Gross examination of tibia and dissection, if needed
Cardiovascular Findings [7]	Childhood or early adulthood	0.4 – 6.4 %	Dissection and examination of the heart. Donor died of a heart attack.
Intervertebral foramen (IVF)[8]	Childhood or early adulthood	3 – 7 %	Dissection of IVF , X-Rays of vertebral column
Scoliosis	Childhood; ages 6 – 10	10 – 25 %	X-Rays
Neurofibromas			
Cutaneous Neurofibromas (Discreet cutaneous and subcutaneous)	Variable; may see increase in number and size during adolescence	0 – 9 yrs 14 % 10 – 19 yrs 44% 20 – 29 yrs 85% > 30 yrs 95%	Dissection and Photographs
Diffuse Plexiform Neurofibromas[10]	Congenital; manifest early in life	25%	Dissection and Photographs
Malignant Peripheral Nerve Sheath Tumors (MPNST)[11]		4 – 13 %	Dissection and examination of abdominal region, extremities, head and neck regions.

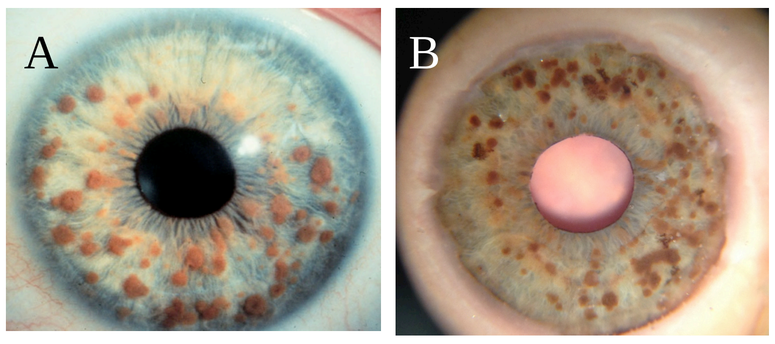
(1 – Debella et al. 2000, 2- Debella et al. 2000; Friedman and Riccardi 1999, 3- Flueler et al. 1986; Huson et al.1987; Lubs et al. 1991, 4- Listernick et al. 1999; Singhal et al. 2002, 5- Riccardi 1999b; Alwan et al. 2005, 6- Crawford and Schorry 1999; Friedman and Birch 1997; Vitale et al. 2002, 7- Carey et al. 1979; Crowe et al. 1956; Lin et al. 2000, 8-, 9- Friedman and Riccardi 1999; Korf and Rubenstein 2005, 10- Walker et al. 2006, 11- Evans et al. 2002; Korf 2000; Levy et al. 2005)

Cutaneous Neurofibromas of NF-1



Discreet neurofibromas are tumors that arise from single peripheral nerves. These dermal tumors usually present themselves just before puberty and tend to increase with age. The quantity and severity of the neurofibromas varies greatly between individuals. The two pictures on the left show different phenotypic severities of NF-1 in patients. (A) Young child displaying characteristic café au lait spots. (B) Older individual with numerous neurofibromas (C and D) Our donor with numerous neurofibromas on both head and torso.

Lisch Nodules

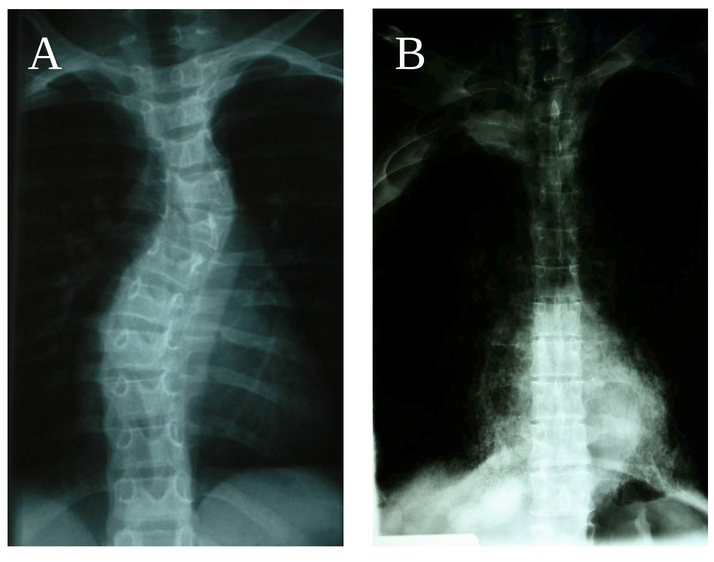


Lisch nodules are the most common clinical feature of NF-1 in adults. Lisch nodules are melanocytic hamartomas that appear as well-defined, dome-shaped elevations projecting from the surface of the iris and are clear to yellow or brown. These tumors are benign and non-obstructive and thus do not impair vision. (A) Iris of a patient with NF-1 with many Lisch nodule. (B) Image of our donor's iris.

Tibial Dysplasia

Tibial dysplasia is rare (1–4% of NF-1 patients). The mechanism by which NF-1 affects bone is unknown. It has been hypothesized that that skeletal malformation might be secondary to endocrine disruption or even a neural tumor invading the bone during growth. (A) X-ray image NF-1 patient with severe tibial dysplasia. (B) X-ray image of the donor's right leg showing no evidence of tibial dysplasia.

Scoliosis



Scoliosis is the most common skeletal finding in NF-1. Dystrophic and non-dystrophic scoliosis are found in patients with NF-1 and are usually present by adolescence. (A) X-ray image of an NF-1 patient with severe scoliosis. (B) X-ray image of the donor showing no signs of a scoliotic curve.

Conclusion

Nuerofibromatosis type 1 is a common genetic disorder that presents with clinical complications the most common include tumors associated with cutaneous nerves and the iris. Other manifestations include tumors in deeper peripheral nerve, cardiac, bone, endocrine and gastrointestinal malformations. It our donor we observed numerous lisch nodules and a severe presentation of cutaneous neurofibromas. Despite the severity of the cutaneous symptoms the donor did not present with any of the common boney malformations. This would suggest that the NF-1 mutation can be very discreet in the tissues in which the mutation is expressed. Future studies will include detailed analysis of the central nervous, cardiac, endocrine and gastrointestinal systems.